Complete Summary

GUIDELINE TITLE

Use of clomiphene citrate in women.

BIBLIOGRAPHIC SOURCE(S)

Use of clomiphene citrate in women. Fertil Steril 2003 Nov;80(5):1302-8. [71 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Ovulatory dysfunction, including anovulation and luteal phase deficiency

GUIDELINE CATEGORY

Diagnosis
Evaluation
Treatment

CLINICAL SPECIALTY

Endocrinology
Family Practice
Internal Medicine
Obstetrics and Gynecology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To describe the pharmacology, mode of action, and indications for clomiphene citrate (CC) treatment
- To outline the pretreatment evaluation, standard and combination treatment regimens, and alternative strategies for the CC-resistant patient
- To summarize the methods for monitoring therapy and review the results, side effects, and risks of CC treatment

TARGET POPULATION

Women with ovulatory dysfunction (anovulation and luteal phase deficiency)

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation

1. Pretreatment evaluation including
    - Basal body temperature recordings
    - Timed serum progesterone determinations
    - Monitoring urinary luteinizing hormone (LH) excretion
    - Timed endometrial biopsy
    - Serial transvaginal ultrasound
2. Detailed medical history
3. Physical examination
4. Screening for hypothyroidism (serum thyroid stimulating hormone [TSH]) and hyperprolactinemia (serum prolactin)
5. Semen analysis in male partner
6. Hysterosalpingography

Treatment

1. Standard therapy using oral clomiphene citrate (CC)
2. Alternative and combination treatment regimens
    - Insulin sensitizing agents (metformin)*
    - Clomiphene and human chorionic gonadotropin (hCG)
    - Clomiphene and glucocorticoids (e.g., dexamethasone or prednisone)
    - Clomiphene and gonadotropins (e.g., menotropins [hMG] or purified or recombinant follicle stimulating hormone [FSH])
    - Ovarian drilling

    *Not currently approved by the Food and Drug Administration (FDA) for this indication

3. Treatment monitoring, including basal body temperature, midcycle luteinizing surge, endometrial biopsy, serial transvaginal ultrasound

MAJOR OUTCOMES CONSIDERED

Ovulation, conception, and pregnancy rates

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This bulletin was approved by the Practice Committee of the American Society for Reproductive Medicine, and the Board of Directors of the American Society for Reproductive Medicine.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Clomiphene citrate (CC) is the best initial treatment for the majority of women whose infertility is associated with ovulatory dysfunction (anovulation, luteal phase deficiency). Combined with appropriately timed intrauterine insemination (IUI), CC treatment also increases cycle fecundity in couples with unexplained infertility.
- CC treatment generally should be limited to the minimum effective dose and to no more than six ovulatory cycles. Failure to conceive after successful CC-induced ovulation is indication for further evaluation to exclude other contributing causes of infertility.
- Combination therapies involving CC and other agents (metformin, glucocorticoids, exogenous gonadotropins) may be effective when treatment with CC alone fails to induce ovulation. Alternative strategies for the CC-resistant woman include treatment with aromatase inhibitors or exogenous gonadotropins and, in selected patients, ovarian drilling.
- CC treatment should be monitored (basal body temperature [BBT], serum progesterone concentration, urinary luteinizing hormone [LH] excretion) to ensure its effectiveness in ovulation induction.
- Side effects of CC treatment are generally mild and well tolerated. The principal risk of CC treatment is an increased incidence of multifetal gestation (<10%).

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Clomiphene citrate (CC) is generally very well tolerated. Some side effects are relatively common, but rarely are they persistent or severe enough to threaten completion of the usual 5-day course or next cycle of treatment. Although CC treatment does have intrinsic risks, they are typically modest and manageable.

POTENTIAL HARMS

Side Effects of Clomiphene Citrate (CC)

- Vasomotor flushes (hot flashes) occur in approximately 10% of CC-treated women, but typically abate soon after treatment ends. Mood swings are also common. Visual disturbances, including blurred or double vision, scotomata, and light sensitivity, are generally uncommon (<2% prevalence) and reversible, although there are isolated reports of persistent symptoms and more severe complications such as optic neuropathy. Whenever visual disturbances are identified, it is prudent to stop treatment and consider alternative methods of ovulation induction. Less specific side effects include breast tenderness, pelvic discomfort, and nausea, all observed in 2% to 5% of CC-treated women.

Multiple Gestation

- Multi-follicular development is relatively common during CC treatment and the risk of multiple gestation is clearly increased to approximately 8% overall. The overwhelming majority of multiple pregnancies that result from CC treatment are twin gestations; triplet and higher order pregnancies are rare but may occur.

Spontaneous Abortion

- Early studies suggested that the incidence of spontaneous abortion in pregnancies resulting from CC treatment was increased over that observed in spontaneous pregnancies. However, a number of more recent studies have described abortion rates that are not different from those observed in spontaneous pregnancies (10% to 15%).

Ovarian Cancer

- Two epidemiologic studies published early in the last decade suggested that the risk of ovarian cancer might be significantly increased in women exposed to ovulation inducing drugs, but subsequent studies have failed to corroborate those findings.

Ovarian Drilling

- A reasonable option for clomiphene-resistant anovulatory women, but the temporary effects of treatment and the risks of postoperative adhesions or diminished ovarian reserve should be carefully considered.

QUALIFYING STATEMENTS

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While this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved

standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources and institutional or clinical practice limitations.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Use of clomiphene citrate in women. Fertil Steril 2003 Nov;80(5):1302-8. [71 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Nov

GUIDELINE DEVELOPER(S)

American Society for Reproductive Medicine - Private Nonprofit Organization

SOURCE(S) OF FUNDING

American Society for Reproductive Medicine

GUIDELINE COMMITTEE

The Practice Committee of the American Society for Reproductive Medicine

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Not stated

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Society for Reproductive Medicine Web site.

Print copies: Available from American Society for Reproductive Medicine, 1209 Montgomery Highway, Birmingham, Alabama 35216-2809; Phone: (205) 978-5000; Fax: (205) 978-5005; E-mail: asrm@asrm.org; Web site: www.asrm.org.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

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Date Modified: 10/9/2006